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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 1103

Application Number: 09/734,786
Filing Date: December 11, 2000
Appellant(s): SAITO ET AL.

James J. Mullen, III, Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 25 August 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The Appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the enablement rejection at issue applies to both groups identified in the appeal brief. Appellant requests that claims directed to *ex vivo* tissue modification and transplantation into a subject (Group I) be adjudicated separately from claims directed to *ex vivo* tissue modification (Group II). Appellant urges that a determination of enablement for one group will not adequately evaluate whether the remaining group is fully enabled.

The Examiner's position is that the grounds upon which the enablement rejection is based apply equally to both of the identified groups. First, as will be discussed in detail below, each of the utilities asserted in the specification involve transplantation of the *ex vivo* modified tissue into a subject. Although the claims embraced by Group II are not limited to transplantation of the modified tissue, using the invention of Group II for the purposes contemplated by the inventor does, in fact, require that transplantation into a subject be enabled. Furthermore, the basis of the enablement rejection is the unpredictability of obtaining transgene expression of sufficient degree and duration, such that the claimed invention can be used for the purposes set forth in the specification. The rejection does not assert that one of ordinary skill would not be able to perform the steps of transplanting genetically modified tissue into a subject, but rather that the disclosure fails to teach the skilled artisan how to make a genetically modified tissue that can be used according to the teachings of the specification. As these grounds apply to the claims of both Groups identified by Appellant, all claims should stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

ALEXEEV et al. Stable and inheritable changes in genotype and phenotype of albino melanocytes induced by an RNA-DNA oligonucleotide. Nat Biotechnol. 1998 Dec;16(13):1343-6

CHOATE et al. Corrective gene transfer in the human skin disorder lamellar ichthyosis. *Nat Med.* 1996 Nov;2(11):1263-7

DENG et al. Sustainable cutaneous gene delivery. *Nat Biotechnol.* 1997 Dec;15(13):1388-91

Li et al. The feasibility of targeted selective gene therapy of the hair follicle. *Nat Med.* 1995 Jul;1(7):705-6

MARSHALL E. Gene therapy's growing pains. *Science.* 1995 Aug 25;269(5227):1050, 1052-5

ORKIN et al. Report and recommendations of the panel to assess the NIH investment in research on gene therapy. 1995, available through NIH and at http://www.nih.gov/news/panelrep.html

ROSS et al. Gene therapy in the United States: a five-year status report. *Hum Gene Ther.* 1996 Sep 10;7(14):1781-90

VERMA et al. Gene therapy -- promises, problems and prospects. *Nature.* 1997 Sep 18;389(6648):239-42

YU et al. Topical gene delivery to murine skin. *J Invest Dermatol.* 1999 Mar;112(3):370-5

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-8, 11, 13-15, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph. This rejection is originally set forth in the prior Office Action, mailed 3 October 2002, beginning at page 6.

Claims 1-8, 11, 13-15, 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

The claims are directed to methods of making and using compositions for treating the mammalian body by means of gene therapy comprising *ex vivo* genetic modification of a histocultured organ or tissue and transplantation of the genetically modified organ or tissue into a recipient animal. Therefore the invention is directed to *ex vivo* gene therapy.

Breadth of the Claims:

The claims encompass a method for delivery of an exogenous nucleic acid in the cell of a mammal *ex vivo*, through genetic modification of a histocultured organ or tissue, and thereby cover all mammals including human beings. The specification teaches that the invention "relates to modifying mammalian subjects to contain heterologous genes" (page 1, lines 7-8). As to the

purpose of modifying said mammalian subjects, the specification teaches: "hair follicles are useful recipients of genes intended to affect the growth or quality of hair, but also are able to produce immunogens and other products that may be useful to the organism taken as a whole. Thus, a transformation of hair follicles can readily be used as an intermediate step in genetic therapy directed to the whole organism" (page 4, lines 20-24); "[s]uitable nucleotide open reading frames include those encoding proteins which elicit immune responses, regulate hair growth, modify hair color, or which are hormones or therapeutic compounds" (page 7, lines 7-9); "it is included within the scope of the invention to modify the metabolism of the subject by, in effect, administering hormones or therapeutic agents such as FSH, LH, human growth hormone, thyroid stimulating hormone, oxytocin, calcitonin, tissue plasminogen activator, erythropoietin, various cytokines such as the interleukins and the like by providing nucleotide sequences that encode them" (page 7, lines 24-29). Thus, the specification clearly indicates that methods of treatment comprising administration of nucleic acids encoding therapeutic proteins is within the scope of the claimed subject matter. Therefore the invention is directed to *ex vivo* gene therapy.

Given that the claims are drawn to a method for therapeutic or vaccination purposes and the composition and methods have no utility other than delivery of exogenous nucleic acids, the intended use for said method is clearly gene therapy.

State of the art:

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor

efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, "...none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Most of the claims of the instant application are directed to compositions and methods for skin based gene therapy. To support the utility of skin based gene therapy, Applicant cites several examples of studies wherein heterologous proteins were expressed in the skin of experimental animals. Applicant cites Choate *et al.* (1996) *Nat Med.* 2:1263-1267 wherein the genetic defect in keratinocytes from lamellar ichthyosis patients was corrected and the corrected keratinocytes produced normal epidermis when transplanted onto nude mice. Applicant also sites Deng *et al.* (1997) *Nat Biotechnol.* 15:1388-1391 as an example of transgene expression via *ex vivo* manipulation of skin cells (i.e. keratinocytes). However, Deng *et al.* also teach that the difficulties encountered in other gene therapy approaches have hindered progress in developing therapies involving gene expression in skin as well, "[w]hile other tissues, such as muscle and

liver, may permit longer-term gene expression by introduced retroviral vectors, epithelial tissues have proven much less tractable in this regard" (page 1389, first paragraph of column 2) and "[w]e have regenerated corrected skin tissue *in vivo* from patients with lamellar ichthyosis and X-linked ichthyosis; however, application of such advances to the treatment of humans was blocked by an inability to sustain transgene expression *in vivo*" (page 1390, first paragraph). These teachings point out both the difficulty in obtaining sustained effective transgene expression in skin, and the unpredictability of extending success in model systems to the clinical setting.

Applicant also cites several examples gene transfer into skin with the goal of vaccinating the host against the transgene. Although the studies cited demonstrate production of antibodies resulting from gene transfer, none provide an example of the immunization sufficient to protect a mammal from a pathogen. One of the studies cited (Yu *et al.* (1999) *J Invest Dermatol.* 112:370-375) concludes with the sentence, "Further studies are required to determine the preclinical utility of this model system" (page 374, final sentence of column 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are: immune responses and the identity of the promoter used to drive gene expression. Verma *et al.* teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma *et al.* further warns that, "... the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and

a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of Direction provided and existence of working examples:

As described above, the prior art teaches a method of transfecting cells and expressing exogenous nucleic acids in mammals through *ex vivo* modification of cells and tissues. However, the prior art does not teach expression of exogenous nucleic acids for the purpose of gene therapy to such levels that a therapeutic effect is obtained. In cases where prior art does not teach how to practice a method, all the guidance must come from the specification. The specification provides guidance for adenovirus-mediated gene transfer of a reporter gene into hair follicles of histocultured mouse skin (see especially Example 1, beginning on page 11), transfer of the modified histocultured skin to a recipient mouse (see especially Example 2, beginning on page 14) and retrovirus mediated gene transfer of a potentially therapeutic gene into histocultured mouse skin. The teachings of the specification do not, however, address the art recognized barriers to achieving successful gene therapy. Transgene expression of the reporter gene *in vivo* was followed for only 10 days (page 15, line 5) and there is no teaching of a therapeutic effect associated with expression of the tyrosinase gene, even in the *in vitro* system. The specification, therefore, provides no guidance with regard to how the teachings can be used in a successful therapy.

Predictability of the Art, Amount of Experimentation and Skill level of the artisan:

While it is relatively routine in the gene transfer art to achieve expression at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Thus, when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product in an art recognized animal model or patient as claimed.

Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention according to its intended purpose. Due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids and the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells using *ex vivo* gene transfer into histocultured organs or tissues, it would require undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in using the claimed methods for the purpose disclosed in the specification. Thus the specification does not enable one skilled in the art to make and use the claimed invention.

(11) Response to Argument

Appellant's position, as it is understood by the Examiner, is that the enablement rejection is improper because the claims are not specifically directed to a therapeutic method. Appellant

does not dispute that achieving therapeutic effect by an *ex vivo* gene therapy method was highly unpredictable at the time of filing. Instead, while acknowledging that claims are to be given their broadest reasonable scope during prosecution, Appellant asserts that one of ordinary skill in the art would readily interpret the pending claims as being directed to methods of genetically modifying tissue *ex vivo* and transplantation of that modified tissue into a mammalian host, and do not require that the *ex vivo* genetic modification produce a therapeutic effect in a host after transplantation. Appellant states, "all the claims require is that the genetic modifications encompassed by the claimed invention merely function as intended to achieve the goals of the claimed methods" (brief, second paragraph on page 5). Appellant urges that because the claims do not recite a therapeutic effect for the genetic modification or the transplantation, the Examiner has erred in reading such a requirement into the pending claims.

These arguments have been fully considered but are not deemed persuasive. As discussed above, the instant claims are broadly directed to introducing a nucleic acid into a mammalian subject or into an intact tissue. In interpreting the claims, it is permissible for the Examiner to consult the specification for guidance as to what Appellant perceives as the scope of the invention (*In re Vogel*, 422 F.2d 438, 441, 164 USPQ 619, 622 (CCPA 1970)). With regard to utility, the primary assertion of the specification is that the claimed invention can be used as part of an *ex vivo* gene therapy approach to the treatment of an essentially unlimited variety of conditions (*Id.*). In particular, the specification teaches, "it is included within the scope of the invention to modify the metabolism of the subject by, in effect, administering hormones or therapeutic agents ... by providing nucleotide sequences that encode them" (page 7, lines 24-29).

Thus, the specification clearly indicates that methods of treatment comprising administration of nucleic acids encoding therapeutic proteins are within the scope of the claimed subject matter.

Beyond treatment, the only other utility contemplated in the specification, is the production of a transgenic subject, which can be used as an experimental model to evaluate the effects of administering other substances (page 9, lines 1-3). However, the production of a useful experimental model, like gene therapy, requires transgene expression at a sufficient level and of sufficient duration to produce a phenotypic change in the genetically modified animal. Therefore, the evidence provided to establish the unpredictability of attaining a therapeutic effect using the claimed invention applies equally to obtaining a phenotypic modification in an experimental animal such that it is a useful experimental model.

Although it is acknowledged that the claims are not limited to a therapeutic method, the specification makes clear that therapeutic methods are within the scope of the claims. Therefore, enablement for the full scope of the claimed subject matter requires enablement for therapeutic application. Furthermore, the specification fails to provide an enabling disclosure for the only application other than gene therapy contemplated therein (i.e., making an animal model) because that too would be expected to requires a level and duration of transgene expression that was not routinely attainable at the time of filing.

Appellant's point that the genetic modifications encompassed by the claimed invention need merely function as intended to achieve the goals of the claimed methods is taken; however, given the high degree of unpredictability in obtaining transgene expression of sufficient level and duration to achieve the goal of therapeutic effect or modified phenotype, the skilled artisan

would have to experiment unduly to achieve the goals set forth in the specification using the claimed method.

Appellant asserts that the pending claims, properly interpreted, relate to methods of genetically modifying tissue *ex vivo* and transplantation of that modified tissue into a mammalian host and that one of ordinary skill in the relevant art would readily be able to practice the full scope of the claimed subject matter without undue experimentation. To support this assertion, Appellant first cites teachings from the prior art characterized in the brief as demonstrating *ex vivo* correction of a tyrosinase gene and *ex vivo* modification of hair follicles. However, teachings of the cited *Nature Biotechnology* article (i.e., Alexeev et al. (1998) *Nature Biotechnol.* 16:1343-1346) are limited to tissue culture and the teachings of the cited *Nature Medicine* article (i.e., Li *et al.* (1995) *Nature Med.* (1995) 1:705-706) merely demonstrate gene transfer of a reporter gene into hair follicles with no suggestion of useful therapeutic effect, or phenotypic modification that would allow one to evaluate the effects of administering other substances to the model system as contemplated in the instant specification. Thus, the art cited does not support the full scope of the claimed method or any method of modifying the metabolism of a subject by administering nucleic acids encoding hormones or therapeutic agents, or production of a transgenic subject which can be used as an experimental model to evaluate the effects of administering other substances.

Appellant next cites Choate *et al.* (1996) *Nature Med* 2: 1263-1267 and Deng *et al.* (1997) *Nature Biotechnol* 15:1388-1391 as teaching successful *ex vivo* modification and transplantation of keratinocytes from patients with lamellar ichthyosis. However, as pointed out in the 3 October 2002 Office Action (paragraph bridging pages 8-9) and reiterated herein above,

Deng *et al.* teaches that it was not possible to obtain transgene expression of sufficient level and duration to achieve a useful therapeutic or phenotypic effect. Specifically, Deng *et al.* states, "[w]e have regenerated corrected skin tissue in vivo from patients with lamellar ichthyosis and X-linked ichthyosis; however, application of such advances to the treatment of humans was blocked by an inability to sustain transgene expression in vivo." Thus, the art cited by Appellant to support enablement of the claims clearly teaches that the technology available as of 1997 could not provide transgene expression of sufficient level and duration to provide a therapeutic effect, at least with respect to lamellar ichthyosis. Given this teaching, the skilled artisan would not expect to be able to affect the growth or quality of hair or modify the metabolism of a subject by administering nucleic acids encoding hormones or therapeutic agents, or to produce a transgenic subject which can be used as an experimental model to evaluate the effects of administering other substances by the claimed method.

Finally, Appellant cites the specification's working examples as perhaps the most compelling guidance regarding how to practice the invention. Appellant asserts: Example 1 discloses detailed guidance regarding the acquisition and *ex vivo* genetic modification of tissue and indicates how the methods encompassed by the pending claims provide an improved method of making *ex vivo* genetic modifications; Example 2 provides detailed guidance regarding how to take tissue genetically modified *ex vivo* and transplant that tissue into a recipient and provides ample guidance regarding how to genetically modify tissue *ex vivo* and transplant that tissue; and Examples 3-8 describe an alternative method to genetically modify tissue *ex vivo*.

However, the working examples stop well short of teaching the skilled artisan how to practice the claimed method to affect the growth or quality of hair or modify the metabolism of a

subject by administering nucleic acids encoding hormones or therapeutic agents, or produce a transgenic subject which can be used as an experimental model to evaluate the effects of administering other substances.

The teachings of Example 1 are limited to *in vitro* modification of histocultured skin to express a GFP transgene. Although the results indicate expression of the reporter gene *in vitro* up to 17 days, expression is assessed by polymerase chain reaction, which would detect expression at levels far below what would be expected to modify the metabolism of a subject or provide a useful experimental model.

Although the teachings of Example 2 demonstrate engraftment of genetically modified histocultured skin in mice, again there is no evidence that the results obtained (i.e., GFP expression detectable by visualization up to 8-days after grafting and up to 10 days by polymerase chain reaction) can be extended to affect the growth or quality of hair or modify the metabolism of a subject by administering nucleic acids encoding hormones or therapeutic agents, or produce a transgenic subject which can be used as an experimental model to evaluate the effects of administering other substances. Likewise, the teachings of Examples 3-8, which describe expression of a tyrosinase gene in histocultured skin *in vitro*, cannot be taken as evidence of enablement for a method that encompasses *ex vivo* gene therapy or the production of genetically modified animals that can be used to evaluate the effects of administering other substances.

While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels, i.e., expression at low levels or at levels providing no useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively

achieve expression of a particular molecule at levels sufficient to effect a useful phenotypic change. As stated in Appellant's brief, "[d]ata presented in the specification indicate that the success of *ex vivo* genetic modification is enhanced by treating the histocultured tissues with collagenase" (page 3). However, it should be pointed out that the enhancement referred to relates to the number of cells that are initially modified. Issues such as level and duration of transgene expression are not addressed by the improvements disclosed in the specification. In particular, although the examples show a 2- to 3-fold increase in the number of hair follicles expressing a GFP transgene with collagenase treatment (see especially Table 1), no data are provided that would indicate that the level of transgene expression is sufficient to provide a useful phenotypic effect. Furthermore, although the specification indicates that there is transgene expression up to 17 days after transduction (paragraph bridging pages 13-14), expression is measured by polymerase chain reaction from reverse transcribed RNA, which is capable of detecting minute levels of transgene expression. Thus, there is no evidence that the claimed method could be applied to a method of treatment or production of a useful transgenic animal as contemplated in the specification.

Appellant's arguments appear to be predicated on the notion that full enablement for claims directed to a method of *ex vivo* gene transfer requires only that the specification teach how to transfer DNA into a cell. However, the first paragraph on 35 USC §112 clearly requires that the specification teach how to make *and* use the claimed invention. In the instant case, the specification provides detailed description of how to practice the claimed method such that a reporter gene can be expressed at some detectable level for a short period of time, but the specification does not teach how to use a method limited to expression of a reporter gene for a

short period of time. The specification also teaches that the claimed method can be used to affect the growth or quality of hair or modify the metabolism of a subject by administering nucleic acids encoding hormones or therapeutic agents, or can be used to produce a transgenic subject, which can be used as an experimental model to evaluate the effects of administering other substances. However, in this case, the art teaches that achieving *in vivo* transgene expression of sufficient level and duration to affect the phenotype of an animal, therapeutically or otherwise, is unpredictable. Given this unpredictability and the failure of the specification to provide teachings that address the many problems that have hindered the development of *ex vivo* gene transfer as a practical therapeutic method, the skilled artisan would have to engage in undue experimentation to extend the teachings of the specification so that the claimed method could be used for the purposes contemplated in the application.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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November 19, 2003

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